REMARKS

STATUS OF THE CLAIMS

Claims 13-20 are pending. Claims 1-12 are canceled. We have amended claim 13 to more clearly define "therapeutic synergy." Support for this amendment is found in the specification at page 5, lines 8-11.

EXAMINER'S OBJECTIONS

The Examiner has objected to claims 2 and 9-11 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has canceled each of these claims.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner has rejected claims 1-10, and 13-20 under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner argues that the term "camptothecin derivative" lacks structural description and the term "topoisomerase II inhibitor" lacks sufficient definition. Applicant respectfully traverses the rejection and submits that the specification particularly points out the intended meaning of both terms.

I. Camptothecin Derivatives

The Examiner argues that in the absence of the specific derivativizations claimed, the metes and bounds of the claimed derivatives cannot be determined. However, here the examiner seems to be confusing breadth with indefiniteness. Camptothecin derivatives are compounds derived from camptothecin. The specification

provides further definition: "(c)amptothecin derivatives are anticancer agents which inhibit topoisomerase I." *Specification*, page 3. Applicants then identify 7 examples of anticancer camptothecin derivatives: irinotecan and derivatives of the structure illustrated on page two of the specification in which X-CO-O- is replaced with a radical - X'R' for which X' is O or S, and R' is a hydrogen atom or an alkyl or acyl radical. Applicants additionally provide twenty three publications describing anticancer camptothecin derivatives appropriate for use in the claimed invention.

The Examiner goes on to argue that the term "camptothecin derivative" is indefinite where Applicant fails to instruct as to how the core compound is modified. Yet, Applicant has provided clear instructions as to how the core compound is modified by describing camptothecin derivatives of the structure illustrated on page 2 of the specification, with the group X-CO-O- located on ring A in position 9, 10, or 11. Each of the derivatives contain modifications of the X-CO-O- group. A person skilled in the art would understand the metes and bounds of the claim with regard to camptothecin derivatives to be compounds of the core compound structure with derivations on the X-CO-O- arm.

Because Applicant provides ample description of the structural modifications claimed, reciting 7 examples and numerous sources for further examples, and provides a description of how the core structure is to be modified, the term "camptothecin derivative" does not render the claims indefinite. Accordingly, Applicant respectfully requests that the Examiner withdraw his indefiniteness rejection to claims 13-20.

II. Topoisomerase II Inhibitor

The Examiner argues that the specification does not provide a standard for ascertaining the requisite degree of anti-topoisomerase II activity to adequately appreciate the scope of the invention, especially in the absence of any indicated name, structure, or form. Applicant respectfully disagrees. Topoisomerase II inhibitor is a term well known in the art of tumor suppression, given to a class of compounds used specifically for regulating tumor growth. The specification lists 2 sub-classes of topoisomerase II inhibitors, anthacycline antibiotics and epipodophyllotoxins, as reference points, and lists specific examples of compounds from each subclass suitable for use in the invention. A person skilled in the art of tumor suppression would not find this term, as used in the specification, to be indefinite. Accordingly, the Applicant respectfully requests that the Examiner withdraw his indefiniteness rejection to claims 13, 14, and 17.

REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-7, 9-12 under 35 U.S.C. §102(b) as anticipated by Furuta *et al.*, *Jpn. J. Cancer Chemother.*, 18(3):393-402, 1991 (hereinafter "Furuta"). Applicant has canceled these claims and therefore this rejection is moot.

REJECTION UNDER 35 U.S.C. § 103

The Examiner has rejected claims 5, 8 and 13-20. Applicant has canceled claims 5 and 8.

To establish a *prima facie* case of obviousness, the reference must teach or suggest all the claim elements or must provide some suggestion or motivation to one of

ordinary skill in the art to modify the reference. Additionally, there must be a reasonable expectation of success. M.P.E.P. § 2143. With respect to claims 13-20, Applicant respectfully traverses the rejection and submits that Furuta would not have rendered obvious the claimed invention.

I. Synergy

The Examiner characterizes the difference between Applicant's claimed method and the method taught by Furuta as merely "the type of tumor that is treated and the for of administration of said agents." *Office Action date May 4, 2004*, page 7. As Applicant has previously argued, Furuta does not teach the therapeutic synergy of the claimed method of treatment. In an effort to expedite prosecution, Applicant has amended claim 13 in response to Examiner's suggestions, to provide the clarity, deliberateness, and precision necessary for acting as her own lexicographer.

The Examiner continues to rely on *Abbott Laboratories v. Syntron Bioresearch, Inc.*, to support his position that the term "synergy" has not been defined with "reasonable clarity, deliberateness, and precision necessary for departure from [the] ordinary meaning." *Abbott Laboratories v. Syntron Bioresearch, Inc.*, 334 F.3d 1343 (Fed. Cir. 2003); Office Action at 7. This case, however, differs from *Abbott*. In *Abbott*, the specification provided two alternative definitions for analyte. *Abbott*, at 1354-55. The court recognized that a patentee may be his own lexicographer (relying on *In re Renishaw*, 158 F.3d 1243 (Fed. Cir. 1998), so long as the term appears with "reasonable clarity, deliberateness, and precision." *Id.* at 1354 citing *In re Paulsen,* 30 F.3d 1475, 1480 (Fed. Cir. 1994). The court held that because two conflicting definitions were provided in the specification for the term "analyte," it therefore did not

appear with reasonable clarity, deliberateness, and precision. Based on this rationale, the court held that the ordinary meaning of the term "analyte" should be used.

The present case is different from *Abbott* because the present specification does not provide, nor does the Examiner assert as much, conflicting definitions for the term "therapeutic synergy." In addition, as previously argued, Applicant has overcome the heavy presumption that the term "synergy" (or "therapeutic synergy") should be given its ordinary and customary meaning, such as the two dictionary definitions previously relied upon by the Examiner. Applicant has acted as her own lexicographer as previously argued in Amendment and Response dated December 3, 2003. (*See also Abbott Laboratories v. Novopharm Ltd.*, 323 F.3d 1324 (Fed. Cir. 2003) (holding that patentee had overcome the presumption that a claim term is given its ordinary and customary meaning because patentee acted as his own lexicographer by providing a definition in the specification).)

Moreover, Applicant has presented arguments, such as those below, distinguishing the claimed invention over the cited art, Furuta, by relying on the definition of synergy (or therapeutic synergy) as defined in the present specification. In essence, Applicant has overcome the heavy presumption that a claim term should be given its ordinary meaning.

Therefore, as argued in previous responses, the Examiner must examine the claims using the definition provided in the specification on page 5, and not the ordinary meaning of the word "synergy" (or "therapeutic synergy") such as those provided in the dictionaries relied upon by the Examiner. The M.P.E.P. and case law discussed above dictate that the Examiner must use that construction when applying art to the claims.

The Examiner's continued failure to follow the M.P.E.P. and the case law is an egregious error.

In view of the definition of "therapeutic synergy," the cited art would not have rendered obvious the claimed invention.

II. Furuta does not teach therapeutic synergy

Although Furuta states that treatment with CPT-11 and adriamycin (*i.e.*, doxorubicin) provides synergistic effects, this reference does not, in fact, disclose a therapeutic synergistic effect as defined in the present specification and presently claimed.

When using one constituent, such as CPT-11, one of ordinary skill in the art would expect that the best result would be achieved at the optimum dose (*i.e.*, maximum tolerated dose or highest non-toxic dose (HNTD)) for that constituent. However, it may be beneficial to a patient to use a smaller dose, possibly, for example, to limit side effects. A therapeutic synergistic combination allows a patient to receive a smaller dose (*i.e.*, less than the HNTD) of one or both constituents and provides results greater than would have been achieved with the HNTD if each constituent had been used individually.

Applicant determined the HNTD for CPT-11 by intravenous (i.v.) and oral routes on various tumors.[1] *See* Specification, page 7, Table I. The HNTD for CPT-11 per os (p.o.) was found to be 806.4 mg/kg (100.8 x 2 times per day x 4 days (6-9)) on PO3 tumors in B6D2F1 mice. *See* Specification, page 11, Table IV.

Additionally, Applicant determined the HNTD for doxorubicin by i.v. on PO3 tumors to be 12.4 mg/kg (6.2 x 2 days of administration). *See* Specification, page 11, Table IV. This result is also consistent with what is known in the art. *See*, for example, Kolfschoten, G. M., *et al.*, Development of a Panel of 15 Human Ovarian Cancer Xenografts for Drug Screening and Determination of the Role of the Glutathione Detoxification System, *Gynecologic oncology*, 76(3):362-8 (2000). This reference reported the HNTD for doxorubicin by i.v. on human ovarian cancer to be 16 mg/kg (8 mg/kg x 2).

After determining the HNTD for each constituent, Applicant combined the constituents to determine if there was a therapeutic synergistic effect, *i.e.*, whether smaller doses of each individual constituent could be used in a composition and yet still achieve a result better than the HNTD of one of the individual constituents when used alone. Applicant demonstrated such a therapeutic synergistic effect in several combinations reported in Table IV on page 11 of the specification.

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1 In the clinic, CPT-11 is generally administered by i.v. and oral routes. The HNTD for CPT-11 by i.v was found to be 346.2 mg/kg in PO3 tumors on B6D2F1 mice. *See* Specification, page 7, Table 1. This HNTD is consistent with what is known in the art. *See*, for example, Chatelut, G. S., *et al.*, Comparison of Intraperitoneal and Intravenous Administration of Irinotecan (CPT-1) in a Murine Peritoneal Colon 26 Model, *Proc. Am. Assoc. Cancer Res.*, 38(3):305 (1997). This reference reported the HNTD of CPT-11 by i.v. administration to be 300 mg/kg. Moreover, the HNTD for intraperitoneal (i.p.) administration of CPT-11 in mice having colon tumors was determined to be 600 mg/kg. *See* Chatelut abstract.

Furuta does not teach the HNTD dose for each individual constituent. In fact, Furuta determined the dose for each constituent not based upon the HNTD for each constituent, but instead used amounts that would produce a desired result, around 150 of the life prolonging rate T/C (%). *See* page 394, first paragraph. For example, Furuta determined that a dose of 37.5 mg/kg (12.5 x 3 days of administration on days 1, 5, 9) of CPT-11 by i.p. administration in mice having L1210 (leukemia) tumors achieved that goal. *See* Table 3. (Applicant notes that this dose is 1/16th of the reported HNTD for i.p. administration of CPT-11 in mice having colon cancer. *See* footnote 2.) Similarly, Furuta determined that a dose of 18.75 mg/kg (6.25 X 3 days of administration on days 1, 5, 9) of doxorubicin i.p. administered in mice having L1210 (leukemia) tumors achieved that goal.[2]

The Examiner continues to argue that the data in Furuta, Table 3, "shows that the effect of two chemicals on the inoculated mice is greater than the effect of each of these chemicals individually" and refers to the example having 37.5 mg/kg CPT-11 (12.5 x 3 days of administration) and 18.75 mg/kg of adriamycin (6.25 x 3 days of administration) producing 16.5 days of survival as exhibiting a synergistic effect. *See* Office Action dated May 4, 2004, at 10 and Experiment 1 in Table A below. Applicant respectfully reiterates that the Examiner's statement is inconsistent with Applicant's definition of therapeutic synergistic effect.

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2 The HNTD for i.p. administration of doxorubicin in mice having lung carcinoma was determined to be 15 mg/kg. *See* Schmid, *et al.*, Differential Uptake of 1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea and Doxorubicin by Lewis Lung Carcinoma and Ridgway Osteoganic Sarcoma, *Cancer-Res.*, 43(3):976-9 (1983).

Moreover, Applicant respectfully submits that the Examiner's statement is not supported by all, and is contrary to some, of the data in Furuta. For ease of understanding, Applicant refers to Table A below. The Examiner's statement that the effect of two chemicals is greater than the effect of each is true for experiment 1, wherein the days of survival are greater when two chemicals are used than the effect of each of these chemicals used individually (experiments 2 and 3). However, the Examiner's statement is contrary to the data in experiment 4 when it is compared to the data in experiment 3. In experiment 4, both chemicals are used and the days of survival are 11.7. In experiment 3, only doxorubicin is used and the days of survival are 11.7. The data in experiments 3 and 4 rebut the Examiner's statement that the effect of two chemicals is greater than the effect of each of these chemicals used individually. The data does not appear to suggest a therapeutic synergistic effect, as defined by the Examiner or, for that matter, the Applicant.

The Examiner's position that side-by-side comparisons are irrelevant due to the varying conditions between experiments contains a logical inconsistency with his earlier argument that the experiment 1 data show a synergistic effect, because this statement, too, is based on side-by-side comparisons. The Examiner either must grant that Furuta's data is inconsistent with regard to therapeutic synergy, or not rely on experiment 1 as an example of Furuta teaching therapeutic synergy.

Table A. Compilation of Data from Four Experiments in Furuta

Experiment	Total Dose of CPT-11 (12.5 mg/kg x 3 days of administration at days 1, 5, 9)	Total Dose of adriamycin (6.25 mg/kg x n days of administration)	Days of Survival
1	37.5	18.75, n=3	16.5
2	37.5	0	10.8
3	0	18.75, n=3	11.7
4	37.5	6.25, n=1	11.7

As further evidence that Furuta does not teach a therapeutic synergistic combination, Applicant refers the Examiner to the rate of survival of the mice in Furuta. Applicant notes that in experiments 2 and 3 in Table A above, the mice treated with one constituent survived about 12 days before they expired. In experiment 1 in Table A, the example relied upon by the Examiner as evidencing a therapeutic synergistic effect, the mice survived about 5 days longer for a total of 17 days.

In comparison, in the examples provided in the present specification in Table IV, the mice treated with CPT-11 alone survived for at least 26 days. (The data in Table IV is not directed to days of survival as in Furuta, but is instead directed to the time in days for the tumors to reach 1000 mg. Therefore, presumably, the mice lived longer than is reported.) The mice treated with doxorubicin alone survived for least 24 days. The mice that were treated with a therapeutic synergistic combination of CPT-11 and doxorubicin survived for at least 52 days. The rate of survival for mice treated with the therapeutic synergistic combination is almost double the rate of survival for the mice treated with the individual constituents alone, and more than three times the rate reported in Furuta. Applicants note that the Examiner failed to respond to this aspect of the response and requests his comments.

Because Furuta does not teach determining the HNTD of either CPT-11 or adriamycin alone, or finding a combination that provides a therapeutic synergistic effect that is superior to one of these compounds, Furuta does not suggest a therapeutic synergistic composition according to the present claims. For at least this reason, Furuta fails to render the presently claimed invention obvious.

III. Furuta does not provide a reasonable expectation of success

Furthermore, in rejecting the claims under 35 U.S.C. § 103(a), the Examiner fails to indicate where or how Furuta provides a reasonable expectation of success in achieving a therapeutic synergistic composition that is useful in treating solid tumors. Furuta discloses treatment of leukemia. Furuta does not disclose or suggest treating solid tumors with CPT-11 and adriamycin. The Examiner minimizes this omission, asserting that one would apply the teachings of Furuta to any type of tumor. Applicant respectfully disagrees.

It is widely recognized in the art of tumor therapy that a treatment regimen that is successful against one type of tumor (*e.g.*, leukemia) will not necessarily be successful against other types of tumors (*e.g.,* solid tumors). For example, L. M. Van Putten teaches that "[i]t is possible that differences in cellular biochemistry may be responsible for explaining the difficulty of treating by means of chemotherapy the majority of solid tumors [as compared to leukemias]." *See* Abstract of L. M. Van Putten, "Recruitment, a double-edged sword in cancer chemotherapy," *Bulletin du Cancer*, 60(2):140-141 (1973). Moreover, it has been noted that "solid tumors are less sensitive to apoptosis induced by anticancer drugs than leukemias and lymphomas." *See* Abstract of M. Kawada, "Development of a Selective Apoptosis Inducer of Solid Tumor Cells,"

Biotherapy, 12(6):967-973 (1998). Copies of both of these references were provided as exhibits attached to the Amendment filed December 3, 2003.

Thus, even assuming for the sake of argument that one were to be motivated by Furuta to apply the teachings of Furuta to other cancers, such as solid tumors, that person would have no reasonable expectation of success in treating the solid tumors. This is especially so because Furuta does not teach or suggest how to determine the HNTD of a treatment compound nor how to use that information to arrive at the most efficacious combination dose of the treatment compounds.

Rather, at most, one of skill in the art would see Furuta as a mere invitation to attempt to treat solid tumors, not a reasonable expectation of success. In other words, any motivation that Furuta might provide would be a motivation to try, not a motivation to succeed. M.P.E.P. § 2145 X.B. prohibits rejections under this theory. Indeed, it is only through the teachings of the present specification that one of ordinary skill in the art would gain a reasonable expectation of success in treating solid tumors with a therapeutic synergistic combination of camptothecin, or a camptothecin derivative, and a topoisomerase II inhibitor. However, Applicant's own disclosure cannot provide the motivation or expectation of success necessary to render a claim obvious.

Therefore, because Furuta does not provide an adequate motivation or reasonable expectation of achieving the presently claimed invention, Applicant respectfully submits that the presently claimed invention would not be obvious over Furuta.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Carol P. Einaudi
Carol P. Einaudi
Reg. No. 32, 220